AD NUMBER

ADB275327

NEW LIMITATION CHANGE

TO

Approved for public release, distribution unlimited

FROM

Distribution authorized to U.S. Gov't. agencies only; Proprietary Info.; Sep 2001. Other requests shall be referred to U.S. Army Medical Research and Materiel Command, 504 Scott St., Ft. Detrick, MD 21702-5012.

AUTHORITY

USAMRMC ltr, dtd 28 July 2003

AD_____

Award Number: DAMD17-00-1-0663

TITLE: Decorin, a Novel Anti-Tumor Agent that Blocks Breast Cancer Growth

PRINCIPAL INVESTIGATOR: Renato V. Iozzo, M.D.

CONTRACTING ORGANIZATION: Thomas Jefferson University
Philadelphia, Pennsylvania

REPORT DATE: September 2001

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

NOTICE

USING GOVERNMENT DRAWINGS, SPECIFICATIONS, OR OTHER DATA INCLUDED IN THIS DOCUMENT FOR ANY PURPOSE OTHER THAN GOVERNMENT PROCUREMENT DOES NOT IN ANY WAY OBLIGATE THE U.S. GOVERNMENT. THE FACT THAT THE GOVERNMENT FORMULATED OR SUPPLIED THE DRAWINGS, SPECIFICATIONS, OR OTHER DATA DOES NOT LICENSE THE HOLDER OR ANY OTHER PERSON OR CORPORATION; OR CONVEY ANY RIGHTS OR PERMISSION TO MANUFACTURE, USE, OR SELL ANY PATENTED INVENTION THAT MAY RELATE TO THEM.

LIMITED RIGHTS LEGEND

Award Number: DAMD17-00-1-0663
Organization: Thomas Jefferson University

Those portions of the technical data contained in this report marked as limited rights data shall not, without the written permission of the above contractor, be (a) released or disclosed outside the government, (b) used by the Government for manufacture or, in the case of computer software documentation, for preparing the same or similar computer software, or (c) used by a party other than the Government, except that the Government may release or disclose technical data to persons outside the Government, or permit the use of technical data by such persons, if (i) such release, disclosure, or use is necessary for emergency repair or overhaul or (ii) is a release or disclosure of technical data (other than detailed manufacturing or process data) to, or use of such data by, a foreign government that is in the interest of the Government and is required for evaluational or informational purposes, provided in either case that such release, disclosure or use is made subject to a prohibition that the person to whom the data is released or disclosed may not further use, release or disclose such data, and the contractor or subcontractor or subcontractor asserting the restriction is notified of such release, disclosure or use. This legend, together with the indications of the portions of this data which are subject to such limitations, shall be included on any reproduction hereof which includes any part of the portions subject to such limitations.

THIS TECHNICAL REPORT HAS BEEN REVIEWED AND IS APPROVED FOR PUBLICATION.

Kath Mone 2/5/02 _____

_____ _____

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	September 2001	Annual (01 Sep 00 - 31 Aug 01)

4. TITLE AND SUBTITLE
Decorin, a Novel Anti-Tumor Agent that Blocks Breast Cancer Growth

5. FUNDING NUMBERS
DAMD17-00-1-0663

6. AUTHOR(S)
Renato V. Iozzo, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Thomas Jefferson University
Philadelphia, Pennsylvania

E-mail: Iozzo@lac.jci.tju.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Distribution authorized to U.S. Government agencies only (proprietary information, Sep 01). Other requests for this document shall be referred to U.S. Army Medical Research and Materiel Command, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

12b. DISTRIBUTION CODE

13. ABSTRACT ***(Maximum 200 Words)***

Decorin is a prototype member of a family of the so-called small leucine-rich proteoglycans. Recent evidence has shown that decorin down-regulates the growth of a variety of tumor cells including breast carcinoma cells. Specifically, we have previously shown that decorin blocks the ErbB2 activity and, therefore, we believe that this is the mechanism that is utilized by decorin-induced growth inhibition. In the past funded year, we have made an attempt to generate adeno-associated viral vector (AAV2) containing decorin. After several negative attempts, we were successful in generating an AAV1-decorin vector. In preliminary studies, we have shown that this vector is capable of transducing various tumor cell lines and generating decorin. We have requested and obtained a one-year, no cost extension to pursue the AAV1 transduction experiments both in vitro and in vivo, in an animal model of orthotopic breast cancer.

14. SUBJECT TERMS
Breast cancer

15. NUMBER OF PAGES
6

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

Table of Contents

INTRODUCTION

Decorin, a prototype member of the small leucine-rich proteoglycan gene family, is emerging as a powerful modulator of cell growth because of its ability to affect matrix assembly, growth factor binding and receptor tyrosine kinase activity. The central hypothesis of our research is that the decorin gene, delivered by adenoviral or adeno associated virus (AAV2) vectors directly to the tumor site, will reduce the growth of solid tumors such as breast , colon and squamous carcinomas (1-5).

BODY OF WORK

In the past year we have worked actively on generating an AAV2 vector containing d the human decorin gene. We have obtained the AAV2-decorin vector and tested on two breast carcinoma cell lines, namely MDA-468 and MDA-453. Unfortunately, after several attempts of transduction with the AAV2-decorin vector, we could not find any expression of decorin either by RT-PCR or Western immunoblotting. We then made another construct in which the vector was changed to AAV1 and was modified to include a 400 bp deletion. Just recently, we found the first evidence for the presence of decorin. Thus we plan to test AAV1-decorin vector in the next year.
We have requested and obtained a one year, no-cost extension from the Department of the Army, in order to continue this project.

KEY RESEARCH ACCOMPLISHMENTS

We were able to generate a vector that could be used in future studies to target breast cancer cells in vivo. This vector is based on the latest generation of AAV1, adeno associated virus 1, which can conceivably induce the expression of decorin in the tumor cells and thus retard the growth of breast carcinoma.
This vector could potentially be delivered systemically

REPORTABLE OUTCOMES

At this moment there are no reportable outcomes.

CONCLUSIONS

We have demonstrated that it is possible to generate an AAV1 vector containing decorin and that this vector can efficiently transduce tumor cell lines. These preliminary studies are encouraging and suggest that we will be able to pursue the study of breast cancer cells *in vitro* and the treatment of animal models of breast cancer as originally planned.

REFERENCES

1. Iozzo, R.V. 1998. Matrix proteoglycans: from molecular design to cellular function. *Annu. Rev. Biochem.* **67**:609-652.

2. Iozzo, R.V., F. Chakrani, D. Perrotti, D.J. McQuillan, T. Skorski, B. Calabretta, and I. Eichstetter. 1999. Cooperative action of germline mutations in decorin and p53 accelerates lymphoma tumorigenesis. *Proc. Natl. Acad. Sci. USA* **96** :3092-3097.

3. Santra, M., D.M. Mann, E.W. Mercer, T. Skorski, B. Calabretta, and R.V. Iozzo. 1997. Ectopic expression of decorin protein core causes a generalized growth suppression in neoplastic cells of various histogenetic origin and requires endogenous p21, an inhibitor of cyclin-dependent kinases. *J. Clin. Invest.* **100**:149-157.

4. Iozzo, R.V., D. Moscatello, D.J. McQuillan, and I. Eichstetter. 1999. Decorin is a biological ligand for the epidermal growth factor receptor. *J. Biol. Chem.* **274**:4489-4492.

5. Santra, M., I. Eichstetter, and R.V. Iozzo. 2000. An anti-oncogenic role for decorin: downregulation of ErbB2 leads to growth suppression and cytodifferentiation of mammary carcinoma cells. *J. Biol. Chem.* **274**:35153-35161.

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 28 July 03

MEMORANDUM FOR Administrator, Defense Technical Information Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for this Command. Request the limited distribution statement for the enclosed accession numbers be changed to "Approved for public release; distribution unlimited." These reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Kristin Morrow at DSN 343-7327 or by e-mail at Kristin.Morrow@det.amedd.army.mil.

FOR THE COMMANDER:

Encl

PHYLIS M. RINEHART
Deputy Chief of Staff for
Information Management

ADB233865
ADB265530
ADB244706
ADB285843
ADB240902
ADB264038
ADB285885
ADB274458
ADB285735
ADB286597
ADB285707
ADB274521
ADB259955
ADB274793
ADB285914
ADB260288
ADB254419
ADB282347
ADB286860
ADB262052
ADB286348
ADB264839
ADB275123
ADB286590
ADB264002
ADB281670
ADB281622
ADB263720
ADB285876
ADB262660
ADB282191
ADB283518
ADB285797
ADB269339
ADB264584
ADB282777
ADB286185
ADB262261
ADB282896
ADB286247
ADB286127
ADB274629
ADB284370
ADB264652
ADB281790
ADB286578
ADB264750
ADB282776
ADB286264
ADB260563
ADB277918
ADB286365
ADB275327
ADB286736
ADB286137
ADB286146
ADB286100
ADB286266
ADB286308
ADB285832